IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	DeStefano, G. et al.)	Confirm. No.:	7531
Serial No.:	10/804,710)	Art Unit:	1616
Filed:	March 19, 2004)	Examiner:	Haghighatian, Mina
For:	Formulation for a metered dose inhaler using hydro-fluoro-alkanes as propellants		
Docket No.:	9/277 (539/168)		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GEORGE DESTEFANO UNDER 37 C.F.R. § 1.132

I, George DeStefano, declare:

1. This declaration is submitted to present evidence in response to the Office Action dated October 4, 2007 in the above-referenced patent application.

2. I am employed at Boehringer Ingelheim Pharmaceuticals, Inc. I am an inventor in the above-referenced patent application.

3. It is noted that the Office Action contains a rejection of claims 5 and 7 under 35 U.S.C. § 103(a) as being unpatentable over Lewis et al. (EP 1219293) in view of Jager et al. (WO 9413262), and of claims 1-7 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Pat. No. 6,423,298 in view of Lewis et al. The documents submitted herein in the attached pages provide additional experimental data showing the criticality of the claimed water content in the claimed formulations.

4. The following Analytical Reports provide support for the criticality of the water content in suspension formulations (Analytical Report, *Results for In Use 6 Hour Delay Single Actuation Reproducibility Study for Ipratropium Bromide/Albuterol Sulfate (HFA-134a) Inhalation Aerosol, with Water Contents Ranging from Inherent Water to 2500ppm,*

File No. AR-030012, February 5, 2003, Boehringer Ingelheim Pharmaceuticals Inc.; Analytical Report, *Evaluation of the Effect of Water on Single Actuation Reproducibility for Ipratropium Bromide/Albuterol Sulfate (HFA-134a) Inhalation Aerosol 0.021/0.120 mg TTV, 10 mL Equipped with the Bespak Valve Actuated using at Patient In-Use Testing Scheme*, Report No. AS/C-03004, January 28, 2003, Boehringer Ingelheim Pharmaceuticals Inc.). The data presented in Report No. AS/C-03004 show that a water concentration of 1500 ppm and greater (equivalent to 0.15% water content) in a suspension formulation containing albuterol sulphate and ipratropium bromide is needed to ensure that the single actuation reproducibility difference does not impact the product (see Abstract, Report No. AS/C-03004). File No. AR-030012 shows that water content of 300 to 1200 ppm (equivalent to 0.03 to 0.12% water content) in a suspension formulation containing albuterol sulphate and ipratropium bromide results in poor reproducibility, while a water content of 1500 to 2500 ppm (equivalent to 0.15 to 0.25% water content) exhibited good reproducibility (page 29, File No. AR-030012). This shows that the water content of the suspension formulation is a critical parameter in the single actuation reproducibility over time.

5. The Analytical Reports demonstrate the criticality of the water content in suspension formulations to achieve single actuation reproducibility of inhalants. The critical range of water content in a suspension formulation containing albuterol sulphate and ipratropium bromide to achieve reproducibility is from 0.13% and 0.25%.

6. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the likes so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

George DeStefano

Date: March 10, 2008

Boehringer Ingelheim

Report Number:

AS/C-03004

ANALYTICAL SCIENCES DEPARTMENT
CONTRACT LABORATORY REPORT

Title:	Evaluation of the Effect of Water on Single Actuation Reproducibility for Ipratropium Bromide/Albuterol Sulfate ( ) Inhalation Aerosol 0.021/0.120 mg TTV, 10 mL Equipped with the Bespak Valve Actuated using at Patient In-Use Testing Scheme

Laboratory:	Cardinal Health RTP	**Report Date:**	Jan. 28, 2003
Product/ Project:	Ipratropium Bromide/Albuterol Sulfate Inhalation Aerosol 0.021/0.120 mg TTV, 10 mL	**BI Project Code:**	
Person Submitting Report for Archival:	Paul D. Curry, Jr., Ph.D.	**Contract Lab Protocol #:**	
		Date Report Archived:	1/29/03

Key Words: Ipratropium Bromide/Albuterol Sulfate (Inhalation Aerosol 0.021/0.120 mg TTV, 10 mL., Effect of Water, Single Actuation Reproducibility, Bespak Valve, Patient In-Use

Abstract:

It is well known that additional water can have a detrmental effect on the performance of non-aqueous suspensions. This study was designed to study the impact of water on single actuation reproducibility (SAR) and to initially indentify a minimum water concentration where the reproducibility is suitable. Other studies have shown low dose delivery for the first shot followed by a higher dose for the second for albuterol sulfate at low water concentrations. The addtion of water to the formulation brings the dose for the individual actuation back to the target delivery. Ipratroprium bromide does not show this behavior because it is in solution in this formulation unlike albuterol sulfafte which is suspended.

This study demonstrates the same behavior. The data would indicate that water concentration of 1500 ppm and greater are needed to ensure that the single actuation reproducibility difference does not impact the product.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7501

Theoretical Water Content: Inherent

Analyst: Brook White

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	115.13	20.56	118.21	20.85	115.17	20.64	117.57	20.63	122.36	21.72
26		113.42	19.74	112.10	19.45	117.79	20.54	117.26	20.34	119.82	21.42
33	SAR	77.03	19.66	66.59	19.61	90.17	19.95	62.84	19.43	82.38	19.42
34		245.57	20.14	202.70	19.47	216.22	19.59	238.14	21.24	214.94	20.25
45-46	Dose	159.74	19.46	139.27	18.83	144.63	19.52	169.23	19.22	149.47	19.76
69	SAR	60.95	19.29	75.53	19.87	76.67	19.34	70.93	18.94	128.19	18.60
70		240.53	20.28	237.87	19.34	256.88	20.88	232.40	20.84	222.82	21.00
105-106	Dose	133.76	19.27	95.46	19.54	95.94	20.03	92.92	19.78	95.99	19.87
129	SAR	169.42[1]	19.62[1]	57.22	19.31	79.18	19.93	69.29	18.84	56.62	18.79
130		161.63[2]	19.62[2]	181.90	19.69	156.13	20.43	177.50	20.78	161.25	19.90
165-166	Dose	103.76	19.55	101.53	19.61	104.51	20.45	100.96	19.96	92.65	19.65
187	SAR	87.58	19.52	58.20	25.05	47.18	19.52	57.62	19.52	92.57	19.22
188		146.99	20.16	168.57	20.82	142.08	21.13	153.97	20.93	136.70	20.66

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	263	257	260	262	265
199-203	364	343	343	331	325

[1]These values were confirmed by reinjection since they were not in trend with the data set. The reinjected samples yielded results of 167.16 and 18.81 µg for Albuterol Sulfate and Ipratropium Bromide respectively.

[2]These values were confirmed by reinjection since they were not in trend with the data set. The reinjected samples yielded results of 160.32 and 19.42 µg for Albuterol Sulfate and Ipratropium Bromide respectively.

Uniformity of Dose Water Challenge

Results reported in µg recovered
Lot Number:
AS Number: 02-10-7501
Theoretical Water Content: Inherent
Analyst: Nichole Bynum

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	114.77	20.55	121.29	21.97	121.85	21.73	115.84	20.69	121.53	21.52
26		119.57	20.87	118.26	20.88	117.92	22.26	121.20	21.46	119.29	21.36
33	SAR	39.60	19.58	47.68	20.48	42.23	20.70	40.38	20.39	47.37	20.29
34		164.26	19.83	155.10	19.75	156.82	19.18	169.58	19.66	156.61	19.84
45-46	Dose	98.77	19.56	99.56	19.85	99.49	20.45	104.71	20.18	98.57	20.05
69	SAR	46.50	19.64	50.50	19.16	41.45	19.82	50.31	20.04	52.55	20.33
70		155.93	19.89	157.65	20.68	159.42	19.32	150.98	18.73	158.94	20.84
105-106	Dose	88.03	18.82	96.15	20.00	94.30	19.59	92.94	19.42	106.61	20.44
129	SAR	51.96	20.29	55.25	20.24	50.28	12.78	89.13	61.90	78.36	17.70
130		150.76	20.17	141.95	19.57	142.01	19.74	130.40	18.61	136.65	20.80
165-166	Dose	94.23	19.57	102.94[2]	17.66[2]	101.73	18.17	99.60[2]	16.83[2]	98.36[2]	16.97[2]
187	SAR	48.15	20.44	60.41	20.65	42.98	20.22	46.04	20.68	60.89	22.05
188		149.23	20.66	140.19	20.92	150.85	21.02	152.92	20.66	138.40	21.78

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	275	270	260	268	279
199-203	341	337	327	330	402[1]

[1]The analyst observed an unusually weak plume for all 5 actuations.

[2]The analyst observed that the first actuation sounded weaker than normal.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7502

Theoretical Water Content: 800ppm

Analyst: Dan Mika

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	116.85	20.57	118.69	20.61	116.57	20.81	117.72	20.74	112.33	19.75
26		116.44	19.92	118.78	20.30	113.46	19.87	118.76	20.62	110.60	19.21
33	SAR	79.59	20.67	92.27	20.84	66.80	20.18	80.28	20.41	69.10	20.04
34		145.92	19.89	140.63	19.98	151.68	20.06	143.55	20.54	145.53	19.59
45-46	Dose	110.49	19.82	108.81	20.23	111.42	20.15	108.24	20.16	106.46	19.49
69	SAR	78.14	20.17	70.83	20.56	108.78	18.75	96.90	19.75	64.81	19.97
70		160.24	20.01	152.88	20.09	140.17	19.52	151.44	19.79	147.23	18.80
105-106	Dose	108.82	19.64	112.10	19.69	109.69	19.58	108.86	19.80	106.69	19.31
129	SAR	68.67	20.47	73.18	20.45	77.48	20.10	72.12	20.29	99.65	18.57
130		156.79	19.58	167.49	20.08	148.12	19.88	154.79	19.99	134.07	18.99
165-166	Dose	112.93	19.43	111.55	18.86	100.26	19.74	104.20	20.03	100.62	19.23
187	SAR	67.20	21.10	103.12	19.25	95.01	20.05	95.15	19.83	92.73	19.36
188		147.90	20.39	124.93	20.32	123.27	19.63	131.34	20.49	116.31	19.92

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	688	722	714	735	686
199-203	762	811	802	821	819

Uniformity of Dose Water Challenge

Results reported in µg recovered
Lot Number:
AS Number: 02-10-7502
Theoretical Water Content: 800ppm
Analyst: Kathryn Johnson

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	115.28	20.70	119.93	21.20	115.46	20.36	113.94	20.15	119.07	21.20
26		114.34	20.09	124.94	20.97	117.20	20.01	118.16	20.34	118.37	20.66
33	SAR	39.99	19.47	41.84	20.47	46.49	19.44	38.20	21.41	43.36	20.82
34		157.71	18.38	164.30	19.43	157.55	19.46	168.46	20.03	166.32	19.99
45-46	Dose	96.73	19.35	92.46	18.89	93.65	19.13	94.80	18.68	100.58	19.88
69	SAR	38.59	19.78	35.71	19.36	49.57	19.41	38.83	19.89	42.23	20.46
70		143.60	18.58	166.93	19.27	150.52	18.93	159.28	19.25	154.28	19.17
105-106	Dose	87.15	17.99	97.51	18.47	91.32	18.18	99.86	18.55	101.10	19.12
129	SAR	42.03	19.87	39.31	20.28	42.43	18.17	34.56	20.05	40.71	20.43
130		138.57	17.76	147.99	18.68	142.98	19.29	150.27	18.49	148.09	20.41
165-166	Dose	89.15	18.04	86.24	18.93	92.27	19.51	88.26	18.65	96.64	18.59
187	SAR	36.33	20.01	37.75	20.06	51.64	20.84	33.77	19.84	44.69	21.23
188		138.95	18.61	148.22	19.36	130.27	19.40	144.81	20.04	142.98	20.05

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	706	699	689	705	674
199-203	776	767	778	788	761

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7503

Theoretical Water Content: 1000ppm

Analyst: Brook White

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	119.53	21.41	115.26	20.43	120.54	21.28	119.53	21.11	119.22	20.97
26		117.87	20.41	118.87	21.03	120.08	20.94	127.94	22.08	122.63	21.68
33	SAR	66.45	20.06	61.57	20.56	68.92	20.67	75.56	21.64	64.60	20.49
34		154.57	21.19	149.77	20.11	147.67	20.40	149.92	20.42	157.16	20.72
45-46	Dose	103.75	20.11	102.91	19.73	106.51	20.53	111.15	20.83	110.27	20.56
69	SAR	60.79	19.61	55.17	19.58	60.55	19.83	62.48	20.96	67.43	19.78
70		152.72	20.44	144.75	19.98	156.18	20.81	157.57	20.73	144.23	20.33
105-106	Dose	112.72	20.10	110.56	20.10	113.97	20.68	114.57	20.73	113.18	20.34
129	SAR	72.77[1]	20.19[1]	57.44	19.53	63.86	19.95	65.41	20.83	66.83	19.98
130		218.36[2]	51.20[2]	141.27	20.17	143.49	20.80	155.02	22.09	147.87	20.91
165-166	Dose	103.11	19.98	101.52	19.97	108.29	20.80	109.34	20.98	103.87	20.32
187	SAR	89.85	19.85	63.00	19.70	67.44	20.67	78.93	22.96	70.80	20.65
188		135.42	21.69	138.18	20.71	140.29	21.73	143.79	21.50	145.14	22.12

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	892	911	919	918	880
199-203	1019	995	1018	1033	983

[1]Data was confirmed by reinjection due to out of trend results for the second actuation of this test. Results of 71.96 and 19.96 µg obtained for Albuterol Sulfate and Ipratropium Bromide respectively.

[2]Data was confirmed by reinjection since it was out of trend with the data set. Results of 214.59 and 49.91 µg were obtained for Albuterol Sulfate and Ipratropium Bromide respectively. Analytical error is suspected but could not be confirmed. The sponsor requested to report the data with no further investigation.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7503

Theoretical Water Content: 1000ppm

Analyst: Nichole Bynum

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	119.34	21.03	117.10	21.04	117.19	20.91	116.11	20.80	115.67	20.69
26		123.22	21.36	116.02	20.31	117.45	20.44	117.78	20.58	118.97	20.92
33	SAR	108.61	20.57	114.23	20.03	113.92	19.80	114.38	20.00	110.03	19.08
34		132.58	20.98	117.31	19.03	114.35	19.27	121.27	19.69	120.60	20.04
45-46	Dose	102.75	20.12	106.17	19.35	110.84	18.77	109.84	19.40	106.21	18.16
69	SAR	39.01	19.73	42.26	19.64	43.31	19.58	49.47	20.20	39.69	19.38
70		168.30	21.82	160.79	19.54	44.79	5.41[1]	152.80	19.17	148.38	18.04
105-106	Dose	116.50	20.06	114.20	19.35	108.99	19.00	113.06	19.37	110.08	18.83
129	SAR	56.87	21.02	96.09	19.72	107.59	20.20	105.46	20.43	87.33	20.02
130		152.62	20.61	128.39	19.42	117.70	19.45	125.52	19.90	134.88	18.48
165-166	Dose	108.03	20.49	117.27	19.70	105.54	19.52	111.27	19.09	111.82	18.53
187	SAR	88.56	20.95	42.13	20.80	53.94	20.73	103.14	20.27	42.25	19.97
188		128.73	20.91	147.33	19.53	146.23	19.64	117.17	20.09	147.48	20.06

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	936	909	886	915	900
199-203	1045	1018	1013	1020	998

[1] This value was lower than expected. However, there was no follow-up investigation of this result. This result was presented to the sponsor. The sponsor had no additional comments.

Uniformity of Dose Water Challenge

Results reported in µg recovered
Lot Number:
AS Number: 02-10-7504
Theoretical Water Content: 1200ppm
Analyst: Dan Mika

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	116.12	20.93	116.98	20.70	117.61	20.87	116.53	20.71	115.57	20.60
26		116.88	20.19	117.37	20.54	117.99	20.42	117.06	20.56	117.26	20.44
33	SAR	115.47	20.64	120.17	20.28	117.21	20.08	116.66	20.77	117.19	23.65
34		117.83	20.07	114.54	20.87	118.94	20.22	120.28	20.56	115.64	20.19
45-46	Dose	111.40	19.73	112.34	26.72	109.13	19.19	113.77	20.06	114.25	19.97
69	SAR	85.73	20.12	100.71	19.82	86.07	20.13	88.78	21.01	94.15	19.54
70		138.10	20.16	123.70	20.33	139.96	20.57	131.06	19.38	132.44	20.56
105-106	Dose	110.05	19.45	110.63	19.63	112.42	19.86	110.90	19.74	110.94	19.75
129	SAR	81.29	19.86	80.29	19.96	88.14	20.50	82.38	19.87	88.28	20.43
130		136.33	19.87	138.94	20.34	140.05	20.22	139.48	20.73	145.92	21.22
165-166	Dose	107.59	19.89	107.69	19.87	108.52	19.97	108.39	20.14	110.74	20.19
187	SAR	113.81	20.29	118.65	20.79	102.22	21.08	97.04	20.54	101.05	20.69
188		117.03	20.89	111.13	20.59	120.00	20.58	127.32	21.03	117.76	20.01

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	1081	1102	1066	1064	1000
199-203	1168	1169	1155	1160	1099

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7504

Theoretical Water Content: 1200ppm

Analyst: Kathryn Johnson

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	116.10	21.10	114.03	20.41	112.53	20.47	114.66	20.89	116.74	20.97
26		113.22	19.97	116.02	20.73	115.40	20.57	118.59	21.44	113.78	20.05
33	SAR	48.49	20.05	67.76	19.86	43.53	18.90	55.28	19.82	58.49	20.20
34		158.76	18.40	155.17	18.98	170.51	19.45	162.81	18.78	157.29	18.99
45-46	Dose	100.66	17.79	104.98	18.43	98.69	17.57	107.29	19.38	103.50	19.15
69	SAR	40.69	19.14	40.95	19.10	50.42	18.85	49.55	19.44	41.17	18.60
70		152.82	17.78	155.40	17.44	147.61	17.45	155.81	19.48	167.65	18.68
105-106	Dose	103.29	17.92	103.79	18.25	102.22	17.79	105.39	18.17	102.98	18.32
129	SAR	52.51	19.10	59.34	19.88	57.51	19.25	75.05	19.87	51.54	19.51
130		138.19	17.26	144.92	19.03	138.06	17.93	133.71	19.07	145.81	18.57
165-166	Dose	93.54	16.06	96.28	16.46	93.60	17.05	99.05	17.39	99.44	17.26
187	SAR	31.05	19.40	34.49	20.21	37.58	18.60	43.68	20.52	31.99	20.24
188		147.05	18.96	151.85	19.20	144.52	18.83	146.22	19.65	148.92	19.78

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	1063	1066	1060	1071	1082
199-203	1159	1173	1154	1175	1184

Uniformity of Dose Water Challenge

Results reported in µg recovered
Lot Number:
AS Number: 02-10-7505
Theoretical Water Content: 1500ppm
Analyst: Brook White

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	116.21	20.67	115.98	20.74	119.88	21.38	126.79	22.26	118.66	21.10
26		118.46	20.67	116.09	20.10	121.20	21.20	122.00	21.34	116.72	20.73
33	SAR	112.55	19.84	116.28	20.82	114.67	20.34	113.06	20.31	114.61	20.86
34		117.06	20.50	111.72	19.32	118.41	20.54	110.90	19.19	115.39	20.39
45-46	Dose	110.45	19.80	111.29	19.78	114.27	20.55	112.32	19.91	113.49	20.17
69	SAR	99.24	19.26	108.44	20.24	99.74	20.02	105.97	20.25	101.45	20.17
70		122.24	20.06	119.12	20.08	124.01	20.35	118.92	19.94	124.88	20.31
105-106	Dose	111.73	20.21	113.12	20.06	113.20	20.48	112.03	19.96	114.97	20.84
129	SAR	113.98	20.14	113.93	19.94	112.79	20.78	110.89	20.07	108.77	19.69
130		118.36	21.38	115.40	20.20	116.83	20.81	115.00	20.45	125.57	22.64
165-166	Dose	107.47	19.95	112.14	20.24	110.44	20.25	109.26	20.24	109.89	20.29
187	SAR	117.19	20.72	119.51	20.61	110.54	20.51	107.43	20.37	119.79	20.74
188		107.92	20.35	114.33	20.87	122.09	22.64	112.39	21.22	117.01	22.25

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	1381	1430	1361	1413	1380
199-203	1488	1488	1438	1503	1486

Uniformity of Dose Water Challenge

Results reported in µg recovered
Lot Number:
AS Number: 02-10-7505
Theoretical Water Content: 1500ppm
Analyst: Nichole Bynum

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	116.73	20.84	117.75	20.66	119.88	20.65	117.66	20.83	125.01	21.96
26		113.69	20.06	115.37	20.18	118.13	20.57	125.89	21.77	124.74	21.81
33	SAR	119.64	22.47	116.18	19.72	118.66	20.09	119.61	20.44	116.61	20.40
34		119.72	19.94	117.46	19.94	118.13	19.56	119.28	19.61	121.44	20.13
45-46	Dose	114.78	19.30	114.70	19.16	108.98	18.65	114.77	19.74	112.26	18.47
69	SAR	112.18	20.14	116.05	19.46	111.63	19.43	114.12	20.20	114.19	19.60
70		122.24	20.85	117.55	19.33	110.99	18.25	118.92	20.47	118.45	18.81
105-106	Dose	116.16	19.95	114.83	19.56	112.33	19.05	112.30	20.42	114.25	19.85
129	SAR	113.66	20.70	109.67	19.65	122.59	19.86	116.34	20.45	112.39	19.84
130		113.45	20.18	121.31	19.92	85.89	14.92	112.48	19.30	121.42	20.02
165-166	Dose	109.10	20.13	108.94	19.64	114.02	18.91	110.36	20.11	115.55	17.60
187	SAR	97.28	20.74	99.90	19.93	105.47	20.31	107.48	20.96	104.49	20.53
188		126.94	21.01	116.29	19.90	111.20	19.25	111.98	20.10	110.54	20.38

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	1367	1393	1369	1428	1381
199-203	1491	1492	1471	1562	1498

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7506

Theoretical Water Content: 2500ppm

Analyst: Dan Mika

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	122.31	20.76	124.15	21.38	119.40	20.64	119.42	20.36	119.08	20.20
26		113.19	20.34	116.23	20.70	116.41	20.91	112.91	20.41	114.47	20.75
33	SAR	119.83	20.11	122.32	21.04	118.66	20.20	117.66	20.03	116.36	20.43
34		111.77	20.44	115.00	20.53	116.50	21.09	111.81	20.13	111.95	20.65
45-46	Dose	113.79	19.84	115.73	20.62	114.49	20.17	110.62	19.64	111.29	20.07
69	SAR	116.56	19.96	122.37	20.74	120.39	20.43	117.88	20.32	120.73	20.49
70		114.39	20.46	112.99	20.27	112.45	20.60	111.14	19.64	108.17	20.23
105-106	Dose	115.43	20.35	117.74	20.53	115.95	20.45	114.04	19.91	112.84	19.81
129	SAR	118.77	20.26	119.46	20.71	118.05	20.49	116.71	19.78	118.50	20.18
130		117.04	21.16	113.68	21.26	115.08	21.15	108.10	20.10	108.95	20.17
165-166	Dose	109.04	20.06	111.09	20.55	108.86	19.84	107.36	19.43	106.84	19.87
187	SAR	112.35	20.52	114.37	20.90	113.56	20.83	112.29	20.10	113.38	20.71
188		109.54	20.86	112.00	21.27	110.88	21.09	106.57	20.69	106.19	21.48

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	2368	2372	2336	2313	2370
199-203	2502	2483	2466	2479	2465

Uniformity of Dose Water Challenge

Results reported in µg recovered
Lot Number:
AS Number: 02-10-7506
Theoretical Water Content: 2500ppm
Analyst: Kathryn Johnson

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	118.31	20.22	121.52	20.71	122.54	21.01	120.44	21.14	119.51	20.58
26		116.30	21.63	115.59	21.24	115.78	20.96	115.26	21.33	118.52	21.78
33	SAR	118.15	19.67	123.20	20.24	108.74	18.68	112.74	18.66	116.39	19.08
34		110.16	19.68	111.55	19.23	123.30	19.05	118.92	19.67	112.31	18.76
45-46	Dose	108.85	19.69	115.19	20.10	109.42	18.35	110.01	18.79	112.51	19.01
69	SAR	114.10	19.92	116.72	20.56	109.25	19.37	110.22	18.85	112.76	20.10
70		108.20	18.66	109.74	18.78	108.62	17.54	110.10	18.58	106.14	19.68
105-106	Dose	103.46	18.53	106.70	19.25	103.64	18.18	104.61	18.86	102.27	18.19
129	SAR	105.51	19.90	106.09	19.84	104.55	19.93	105.78	19.51	107.21	19.65
130		104.97	19.09	106.68	19.73	111.66	18.76	106.94	19.75	108.97	19.96
165-166	Dose	95.47	18.82	99.41	19.17	96.08	17.84	98.80	19.22	94.20	18.74
187	SAR	100.26	21.00	101.76	20.59	97.34	20.18	98.89	20.03	93.45	20.01
188		95.69	20.01	95.40	20.51	102.57	18.92	97.96	20.08	92.92	19.25

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	2362	2356	2327	2306	2346
199-203	2473	2499	2436	2460	2488

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7507

Theoretical Water Content: 3000ppm

Analyst: Brook White

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	116.79	20.63	118.78	20.84	114.65	19.88	115.17	20.26	114.81	20.36
26		116.64	20.34	114.57	20.24	113.22	20.02	117.60	21.12	114.75	20.95
33	SAR	116.12	20.18	114.51	19.30	111.95	19.23	116.47	20.44	114.74	20.25
34		115.87	20.62	113.18	19.59	109.45	19.21	113.72	20.14	112.13	19.84
45-46	Dose	113.55	20.27	111.76	19.86	110.04	19.66	112.80	20.11	110.32	19.90
69	SAR	109.91	19.33	114.65	20.07	109.43	18.77	114.66	19.86	113.59	20.15
70		110.79	20.15	111.36	19.66	108.25	19.50	108.31	19.41	112.30	19.95
105-106	Dose	106.24	19.04	105.50	18.97	104.43	18.94	108.74	19.63	105.61	19.64
129	SAR	111.53	19.66	112.73	20.08	108.28	19.39	112.30	19.79	111.44	19.67
130		111.51	20.43	112.78	20.33	107.66	19.59	110.29	20.15	111.13	20.54
165-166	Dose	104.08	19.03	105.03	19.81	102.79	19.27	106.09	20.13	101.12	19.55
187	SAR	105.30	19.64	106.67	20.02	105.85	19.30	108.70	20.34	104.53	20.37
188		108.80	21.15	105.98	20.34	102.38	20.16	109.39	21.92	106.77	21.39

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	2880	2897	2847	2812	3071
199-203	3072	3059	3016	3040	3304

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7507

Theoretical Water Content: 3000ppm

Analyst: Kathryn Johnson

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	115.63	20.16	113.86	19.80	116.54	20.24	112.98	19.99	115.98	20.94
26		107.23	19.69	107.73	19.16	115.93	20.91	111.69	20.12	111.83	20.05
33	SAR	115.88	19.98	114.25	19.05	114.43	19.24	113.75	18.92	114.69	19.39
34		105.62	17.80	108.54	17.95	114.01	18.69	112.02	18.30	111.47	18.97
45-46	Dose	103.31	17.63	104.60	17.76	109.46	18.27	105.77	17.84	104.59	17.82
69	SAR	101.08	19.01	106.33	18.83	107.76	19.42	108.06	19.17	107.30	19.12
70		108.12	17.37	106.76	17.85	113.24[1]	18.66[1]	108.54	19.06	104.75	18.35
105-106	Dose	101.02	17.35	102.02	18.07	103.96	17.68	102.51	18.06	101.53	18.08
129	SAR	103.08	19.77	103.14	18.08	102.88	19.45	108.60	19.57	104.96	19.51
130		106.76	17.27	108.04	18.54	115.61	19.45	102.71	18.65	103.97	18.55
165-166	Dose	90.88	12.85	70.26	8.52	87.87	10.13	89.64	12.38	89.04	13.95
187	SAR	96.45	19.42	90.68	19.05	87.57	19.62	87.02	19.59	86.35	19.42
188		88.82	18.99	90.26	18.84	100.53	20.92	91.29	19.42	80.36	19.44

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	2795	2855	2831	2805	2841
199-203	2956	3049	3004	2976	3008

[1]Analyst observed that this actuation sounded weaker than normal.

Uniformity of Dose Water Challenge

Results reported in µg recovered
Lot Number:
AS Number: 02-10-7508
Theoretical Water Content: 3500ppm
Analyst: Brook White

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	119.26	21.31	114.26	20.00	113.72	20.20	109.36	19.76	111.63	19.84
26		116.90	20.55	104.49	19.16	108.69	19.55	115.32	20.69	112.33	19.77
33	SAR	109.74	19.54	115.38	20.34	110.26	19.76	111.04	19.22	114.81	20.06
34		114.78	20.54	109.11	20.00	110.68	19.26	113.07	20.00	114.46	20.74
45-46	Dose	108.77	19.61	106.58	19.62	106.91	19.52	108.66	20.02	108.71	19.72
69	SAR	110.32	19.31	111.13	20.05	103.45	19.29	108.26	19.49	110.96	19.65
70		110.29	20.28	109.88	19.94	108.21	20.05	108.26	20.34	113.82	20.50
105-106	Dose	102.54	18.78	105.92	19.36	103.81	19.46	104.38	19.32	105.34	19.46
129	SAR	112.03	20.40	108.01	19.88	107.55	20.08	105.69	19.45	109.58	20.01
130		110.87	20.93	109.67	20.58	108.77	20.84	108.23	19.97	106.11	19.70
165-166	Dose	101.92	19.77	98.75	19.31	97.24	18.46	100.21	19.81	100.89	19.01
187	SAR	102.85	20.05	104.49	20.09	106.31	20.19	99.75	19.07	105.50	19.50
188		104.69	21.04	99.83	20.07	103.75	21.25	101.51	21.24	99.90	20.54

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuations	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	3416	3352	3367	3320	3302
199-203	3533	3556	3558	3540	3551

Uniformity of Dose Water Challenge

Results reported in µg recovered
Lot Number:
AS Number: 02-10-7508
Theoretical Water Content: 3500ppm
Analyst: Kathryn Johnson

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9[1]		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	112.02	20.13	114.41	19.95	115.22	19.99	117.50	20.48	116.70	20.62
26		108.44	19.80	114.58	21.22	109.67	20.27	109.60	20.23	107.58	19.57
33	SAR	109.10	18.51	109.33	18.95	117.84	20.51	112.49	18.89	110.15	19.19
34		110.44	18.09	100.80	19.74	106.24	19.27	111.46	18.80	116.55	18.97
45-46	Dose	105.40	18.21	99.55	17.22	109.68	19.51	106.55	17.97	108.31	18.30
69	SAR	101.42	18.98	102.63	18.04	104.06	18.76	104.88	17.15	103.54	19.23
70		105.25	17.95	103.34	17.65	114.88	18.83	105.91	17.79	117.73	19.08
105-106	Dose	101.56	18.03	101.28	17.68	105.87	18.39	103.37	17.85	104.14	17.96
129	SAR	96.51	19.09	98.10	17.55	101.57	18.96	99.14	18.12	103.08	19.85
130		106.27	18.53	98.85	17.92	112.53	19.76	101.08	19.14	107.76	18.90
165-166	Dose	88.29	12.23	85.45	11.54	92.06	13.77	91.10	13.67	92.48	14.08
187	SAR	90.87	19.18	94.74	19.23	98.05	19.83	87.74	19.18	91.15	20.00
188		84.44	19.42	85.29	19.97	86.82	19.65	81.18	19.60	83.01	19.58

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuations	Can 6	Can 7	Can 8	Can 9[1]	Can 10
16-20	3360	3381	3404	3396	3365
199-203	3528	3360	3572	3567	3551

[1]During initial water content testing, 6 actuations may have been made (16-21 actuations), Sponsor was notified.

Uniformity of Dose Water Challenge
Results reported in µg recovered
Lot Number:
AS Number: 02-10-7509
Theoretical Water Content: 4000ppm
Analyst: Brook White

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	111.00	20.05	111.12	20.08	107.69	19.85	109.37	19.78	109.83	20.26
26		114.93	19.82	108.69	19.84	105.13	19.80	111.82	20.29	109.57	20.61
33	SAR	111.64	19.64	108.50	19.29	107.54	19.66	109.40	19.63	112.92	20.30
34		108.96	19.71	103.73	19.06	103.49	19.75	110.56	19.85	109.26	20.35
45-46	Dose	105.70	19.34	107.09	19.33	103.04	18.84	107.71	19.52	108.75	20.06
69	SAR	107.67	19.19	108.24	19.42	103.84	19.33	103.61	19.28	109.93	19.81
70		110.99	19.80	106.52	20.27	100.93	18.86	109.04	20.61	107.58	20.24
105-106	Dose	103.56	18.83	102.73	19.31	101.74	19.22	104.33	19.37	107.92	19.91
129	SAR	108.69	19.43	106.55	19.37	103.40	19.04	106.54	20.05	110.48	20.40
130		105.58	20.83	105.30	20.37	97.61	18.90	102.24	19.86	107.98	20.88
165-166	Dose	93.00	18.04	95.39	19.28	91.81	18.85	95.40	19.48	99.05	19.48
187	SAR	99.14	20.18	96.00	19.67	97.45	19.73	98.47	19.44	97.47	19.54
188		94.35	20.32	93.34	20.10	95.22	20.11	96.11	21.03	99.88	21.63

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	3805	3822	3843	3754	3811
199-203	4045	4003	4033	3938	4014

Uniformity of Dose Water Challenge
Results reported in µg recovered
Lot Number:
AS Number: 02-10-7509
Theoretical Water Content: 4000ppm
Analyst: Kathryn Johnson

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	116.70	20.77	110.63	19.79	109.67	19.99	108.48	19.93	113.94	20.11
26		110.22	20.49	110.25	20.45	108.48	20.01	110.55	20.52	107.93	20.42
33	SAR	104.40	18.46	107.39	18.49	101.89	18.89	99.49	18.78	101.71	18.83
34		112.67	17.93	112.71	17.96	113.58	17.39	110.43	17.55	109.57	17.68
45-46	Dose	107.88	18.44	104.94	17.04	103.43	17.40	102.29	17.56	101.34	17.57
69	SAR	98.58	19.10	91.55	15.39	95.34	17.19	92.18	16.41	95.75	16.97
70		118.85	18.97	117.62	19.28	116.26	18.73	110.24	18.37	113.12	18.90
105-106	Dose	103.70	18.06	96.35	15.50	97.83	15.05	95.71	15.62	97.11	16.02
129	SAR	99.24	19.76	93.70	18.79	94.21	18.95	88.04	18.29	94.86	19.32
130		106.17	18.91	109.41	18.80	107.94	19.14	108.32	19.36	107.04	19.00
165-166	Dose	80.34	10.28	87.96	12.20	91.87	14.17	85.50	13.57	87.78	12.70
187	SAR	81.95	19.26	73.03	17.19	76.95	17.66	75.68	19.52	80.47	18.37
188		74.83	19.48	85.99	18.39	87.35	19.29	66.70	18.68	89.32	20.28

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	3815	3741	3760	3829	3708
199-203	3995	3963	3958[1]	4030	3925

[1]This canister was inadvertantly tested at actuations 200-204.

I. Purpose

The purpose of this study is to examine the effects of water content in Ipratropium Bromide/Albuterol Sulfate 0.021/0.120 mg TTV, 10 mL Inhalation Aerosol on testing for Single Actuation and Dose (2 actuations) through life (ca. 200 actuations).

II. Applicable Regulatory Requirements

This study will be conducted as per GMP (21 CFR 210 and 211) regulations.

III. Materials

BIPI will manufacture canisters using the same formulation but different water contents. The samples will be grouped as follows.

AS Testing Number	Lot Number	Target ppm Water
02-10-7501	A1	Inherent*
02-10-7502	A2	800*
02-10-7503	A3	1000*
02-10-7504	A4	1200*
02-10-7505	A5	1500*
02-10-7506	A6	2500*
02-10-7507	A7	3000
02-10-7508	A8	3500
02-10-7509	B8	4000

IV. Study Design

A total of 90 canisters will be tested utilizing the following table. Ten (10) canisters will be selected from each lot, Five (5) to be stored in an upright orientation and Five (5) in an inverted orientation. Canisters will be placed in orientation immediately following initial Water Content testing and will be stored and weighed in their designated orientation throughout the study life.

Water Content testing will be performed at the beginning and end of the study per the following table. Initial Water Content testing will occur no earlier than the Friday prior initiation of the testing schedule. If the initial Water Content is performed on the preceding Friday, then conduct testing as indicated for Beginning Testing Option 1. Otherwise, proceed as indicated in Beginning Testing Option 2.

* Priority sample, test before other samples.

Final Water Content testing may occur as late as the Monday following the end of the study, if necessary. No change to the testing scheme below will be needed if testing is delayed for final Water Content.

For all methods, calculate sample weights as follows: **W1-W2= Sample Weight**
W2 is the canister weight recorded immediately following each test point and W1 is the canister weight prior to testing (previous timepoint's W2.)

Wasting actuations will be performed using a jar and baseplate. A delay of no less than 2 hours must occur between completion of previous wasting timepoint and initiation of next wasting timepoint when multiple wasting sessions are required on the same day. The firing and shaking of canisters is to be performed as outlined in the Uniformity of Dose procedure for wasting canisters. A swab will be used to thoroughly clean the interior of the valve stem prior to collecting the final weight for both the Water Content and the Wasting steps. It is critical to clean the valve stem while the interior is still wet from the testing step. Wasting will be performed per the following table.

Samples must equilibrate for 24 hours before any Uniformity of Dose sampling can be performed. The single actuation reproducibility protocol (SAR) requires that two single actuations be collected in separate containers where indicated. Do not shake canisters between actuations for the SAR protocol. Uniformity of Dose samples will be collected per the following table.

Record testing times as follows:

Water Content testing: It is not necessary to record testing times.
Uniformity of Dose/SAR testing: Record time testing was initiated.
Wasting: Record the time testing was initiated and completed.

Beginning Testing Option 1: Water Content testing performed on preceding Friday

Week 1		
Day	**Actuation Number**	**Action**
Preceding Friday	1-5	Priming
	6-15	Clearing the Inlet Tube (Water Content)
	16-20	Water Content Sample
Monday	21-24	Priming
	25 & 26	**0 hr SAR** **Shot weight collection**
	27-32	Actuate to waste after 0 hr SAR **Shot weight collection**

Then continue with testing as indicated below for Week 1 Tuesday.

Beginning Testing Option 2: Water Content testing performed on preceding Friday

Week 1		
Day	**Actuation Number**	**Action**
Monday	1-5*	Priming
	6-15*	Clearing the Inlet Tube (Water Content)
	16-20*	Water Content Sample
	21 & 22	**0 hr SAR** **Shot weight collection**
	23-32	Actuate to waste after 0 hr SAR **Shot weight collection**

Then continue with testing as indicated below for Week 1 Tuesday.

Week 1		
Day	**Actuation Number**	**Action**
Tuesday	**33 & 34****	**24 hr SAR** **Shot weight collection**
	35-44	Actuate to waste after 24 hr SAR **Shot weight collection**
Wednesday	**45-46****	**24 hr Dose** **Shot weight collection**
	47-48	Actuate to waste after Dose **Shot weight collection**
	49-52	Actuate to waste Mid Day **Shot weight collection**
	53-56	Actuate to waste End Day **Shot weight collection**
Thursday	57-68	Actuate to waste **Shot weight collection**
Friday	**69 & 70****	**24 hr SAR** **Shot weight collection**
	71-72	Actuate to waste after 24 hr SAR (actuations 69 & 70) **Shot weight collection**
	73-76	Actuate to waste Mid Day **Shot weight collection**
	77-80	Actuate to waste End Day **Shot weight collection**

* May be performed as early as the Friday prior.
** Must occur at least 24 hours from completion of prior wasting timepoint.

Week 2		
Day	**Actuation Number**	**Action**
Monday	81-84	Actuate to waste Beg Day **Shot weight collection**
	85-88	Actuate to waste Mid Day **Shot weight collection**
	89-92	Actuate to waste End Day **Shot weight collection**
Tuesday	93-104	Actuate to waste **Shot weight collection**
Wednesday	**105-106**[**]	**24 hr Dose** **Shot weight collection**
	107-108	Actuate to waste after 24 hr Dose (actuations 105 & 106) **Shot weight collection**
	109-112	Actuate to waste Mid Day **Shot weight collection**
	113-116	Actuate to waste End Day **Shot weight collection**
Thursday	117-128	Actuate to waste **Shot weight collection**
Friday	**129 & 130**[**]	**24 hr SAR** **Shot weight collection**
	131-132	Actuate to waste after 24 hr SAR (actuations 129 & 130) **Shot weight collection**
	133-136	Actuate to waste Mid Day **Shot weight collection**
	137-140	Actuate to waste End Day **Shot weight collection**

[**] Must occur at least 24 hours from completion of prior wasting timepoint.

Week 3		
Day	**Actuation Number**	**Action**
Monday	141-144	Actuate to waste Beg Day **Shot weight collection**
	145-148	Actuate to waste Mid Day **Shot weight collection**
	149-152	Actuate to waste End Day **Shot weight collection**
Tuesday	153-164	Actuate to waste **Shot weight collection**
Wednesday	**165-166****	**24 hr Dose** **Shot weight collection**
	167-168	Actuate to waste after 24 hr Dose (actuations 165 & 166) **Shot weight collection**
	169-172	Actuate to waste Mid Day **Shot weight collection**
	173-174	Actuate to waste End Day **Shot weight collection**
Thursday	175-186	Actuate to waste **Shot weight collection**
Friday	**187 & 188****	**24 hr SAR** **Shot weight collection**
	189-198 *	Clear sample inlet tube (Water Content)
	199-203 *	Water Content Sample

V. Test Methods

Method	ATM #	BIPI TP #	Method Transfer
Water	ATM-		TTP-
Uniformity of Dose	ATM-		TTP-

VI. Reporting

Report the data using the Access Database provided in a Certificate of Analysis format. An electronic copy of the data should also be provided.

VII. Attachments

None.

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* May be performed as late as the Monday following the last SAR.
** Must occur at least 24 hours from completion of prior wasting timepoint.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7501

Theoretical Water Content: Inherent

Analyst: Brook White

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	115.13	20.56	118.21	20.85	115.17	20.64	117.57	20.63	122.36	21.72
26		113.42	19.74	112.10	19.45	117.79	20.54	117.26	20.34	119.82	21.42
33	SAR	77.03	19.66	66.59	19.61	90.17	19.95	62.84	19.43	82.38	19.42
34		245.57	20.14	202.70	19.47	216.22	19.59	238.14	21.24	214.94	20.25
45-46	Dose	159.74	19.46	139.27	18.83	144.63	19.52	169.23	19.22	149.47	19.76
69	SAR	60.95	19.29	75.53	19.87	76.67	19.34	70.93	18.94	128.19	18.60
70		240.53	20.28	237.87	19.34	256.88	20.88	232.40	20.84	222.82	21.00
105-106	Dose	133.76	19.27	95.46	19.54	95.94	20.03	92.92	19.78	95.99	19.87
129	SAR	169.42[1]	19.62[1]	57.22	19.31	79.18	19.93	69.29	18.84	56.62	18.79
130		161.63[2]	19.62[2]	181.90	19.69	156.13	20.43	177.50	20.78	161.25	19.90
165-166	Dose	103.76	19.55	101.53	19.61	104.51	20.45	100.96	19.96	92.65	19.65
187	SAR	87.58	19.52	58.20	25.05	47.18	19.52	57.62	19.52	92.57	19.22
188		146.99	20.16	168.57	20.82	142.08	21.13	153.97	20.93	136.70	20.66

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	263	257	260	262	265
199-203	364	343	343	331	325

[1]These values were confirmed by reinjection since they were not in trend with the data set. The reinjected samples yielded results of 167.16 and 18.81 µg for Albuterol Sulfate and Ipratropium Bromide respectively.

[2]These values were confirmed by reinjection since they were not in trend with the data set. The reinjected samples yielded results of 160.32 and 19.42 µg for Albuterol Sulfate and Ipratropium Bromide respectively.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7501

Theoretical Water Content: Inherent

Analyst: Nichole Bynum

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	114.77	20.55	121.29	21.97	121.85	21.73	115.84	20.69	121.53	21.52
26		119.57	20.87	118.26	20.88	117.92	22.26	121.20	21.46	119.29	21.36
33	SAR	39.60	19.58	47.68	20.48	42.23	20.70	40.38	20.39	47.37	20.29
34		164.26	19.83	155.10	19.75	156.82	19.18	169.58	19.66	156.61	19.84
45-46	Dose	98.77	19.56	99.56	19.85	99.49	20.45	104.71	20.18	98.57	20.05
69	SAR	46.50	19.64	50.50	19.16	41.45	19.82	50.31	20.04	52.55	20.33
70		155.93	19.89	157.65	20.68	159.42	19.32	150.98	18.73	158.94	20.84
105-106	Dose	88.03	18.82	96.15	20.00	94.30	19.59	92.94	19.42	106.61	20.44
129	SAR	51.96	20.29	55.25	20.24	77.68	20.06	89.13	61.90	78.36	17.70
130		150.76	20.17	141.95	19.57	142.01	19.74	130.40	18.61	136.65	20.80
165-166	Dose	94.23	19.57	102.94[2]	17.66[2]	101.73	18.17	99.60[2]	16.83[2]	98.36[2]	16.97[2]
187	SAR	48.15	20.44	60.41	20.65	42.98	20.22	46.04	20.68	60.89	22.05
188		149.23	20.66	140.19	20.92	150.85	21.02	152.92	20.66	138.40	21.78

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	275	270	260	268	279
199-203	341	337	327	330	402[1]

[1]The analyst observed an unusually weak plume for all 5 actuations.

[2]The analyst observed that the first actuation sounded weaker than normal.

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7505

Theoretical Water Content: 1500ppm

Analyst: Brook White

Actuation Number	Test	Inverted									
		Can 1		Can 2		Can 3		Can 4		Can 5	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	116.21	20.67	115.98	20.74	119.88	21.38	126.79	22.26	118.66	21.10
26		118.46	20.67	116.09	20.10	121.20	21.20	122.00	21.34	116.72	20.73
33	SAR	112.55	19.84	116.28	20.82	114.67	20.34	113.06	20.31	114.61	20.86
34		117.06	20.50	111.72	19.32	118.41	20.54	110.90	19.19	115.39	20.39
45-46	Dose	110.45	19.80	111.29	19.78	114.27	20.55	112.32	19.91	113.49	20.17
69	SAR	99.24	19.26	108.44	20.24	99.74	20.02	105.97	20.25	101.45	20.17
70		122.24	20.06	119.12	20.08	124.01	20.35	118.92	19.94	124.88	20.31
105-106	Dose	111.73	20.21	113.12	20.06	113.20	20.48	112.03	19.96	114.97	20.84
129	SAR	113.98	20.14	113.93	19.94	112.79	20.78	110.89	20.07	108.77	19.69
130		118.36	21.38	115.40	20.20	116.83	20.81	115.00	20.45	125.57	22.64
165-166	Dose	107.47	19.95	112.14	20.24	110.44	20.25	109.26	20.24	109.89	20.29
187	SAR	117.19	20.72	119.51	20.61	110.54	20.51	107.43	20.37	119.79	20.74
188		107.92	20.35	114.33	20.87	122.09	22.64	112.39	21.22	117.01	22.25

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 1	Can 2	Can 3	Can 4	Can 5
16-20	1381	1430	1361	1413	1380
199-203	1488	1488	1438	1503	1486

Uniformity of Dose Water Challenge

Results reported in µg recovered

Lot Number:

AS Number: 02-10-7505

Theoretical Water Content: 1500ppm

Analyst: Nichole Bynum

Actuation Number	Test	Upright									
		Can 6		Can 7		Can 8		Can 9		Can 10	
		Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB	Alb SO4	IPB
25	SAR	116.73	20.84	117.75	20.66	119.88	20.65	117.66	20.83	125.01	21.96
26		113.69	20.06	115.37	20.18	118.13	20.57	125.89	21.77	124.74	21.81
33	SAR	119.64	22.47	116.18	19.72	118.66	20.09	119.61	20.44	116.61	20.40
34		119.72	19.94	117.46	19.94	118.13	19.56	119.28	19.61	121.44	20.13
45-46	Dose	114.78	19.30	114.70	19.16	108.98	18.65	114.77	19.74	112.26	18.47
69	SAR	112.18	20.14	116.05	19.46	111.63	19.43	114.12	20.20	114.19	19.60
70		122.24	20.85	117.55	19.33	110.99	18.25	118.92	20.47	118.45	18.81
105-106	Dose	116.16	19.95	114.83	19.56	112.33	19.05	112.30	20.42	114.25	19.85
129	SAR	113.66	20.70	109.67	19.65	122.59	19.86	116.34	20.45	112.39	19.84
130		113.45	20.18	121.31	19.92	109.40	18.51	112.48	19.30	121.42	20.02
165-166	Dose	109.10	20.13	108.94	19.64	114.02	18.91	110.36	20.11	115.55	17.60
187	SAR	97.28	20.74	99.90	19.93	105.47	20.31	107.48	20.96	104.49	20.53
188		126.94	21.01	116.29	19.90	111.20	19.25	111.98	20.10	110.54	20.38

Alb SO4 = Albuterol Sulfate IPB = Ipratropium Bromide SAR = Single Actuation Reproducibility

Water Content (ppm)

Actuation	Can 6	Can 7	Can 8	Can 9	Can 10
16-20	1367	1393	1369	1428	1381
199-203	1491	1492	1471	1562	1498

Boehringer Ingelheim

ANALYTICAL SCIENCES DEPARTMENT **ANALYTICAL REPORT**

Title: Results for In Use 6 Hour Delay Single Actuation Reproducibility Study for Ipratropium Bromide/Albuterol Sulfate Inhalation Aerosol, with Water Contents Ranging from Inherent Water to 2500 ppm

Author(s): Johanna Ubben	**Date of Report:** 05 Feb 2003
Product / Project:	**Project Code:** BP

Requester: George DeStefano

cc: P. D. Curry, Jr, Ph.D.; E. Gump, Ph.D.; R. Patel, Ph.D.

Sample ID: 02-10-7515, 02-10-7516, 02-10-7517, 02-10-7518, 02-10,7519, 02-10-7520

Key Words: Combivent HFA, dose uniformity, water content, single actuation reproducibility, valve delivery through life, total can assay

File Number: AR-030012	**Security:** Read Only

Signature: Johanna Ubben Feb 21, 2003

Verification: Feb. 21, 2003

Data Reference(s): 5886/083

I. Introduction

Samples from Ipratropium Bromide/Albuterol Sulfate Inhalation Aerosol, Lot were submitted to the Pulmonary Analysis Laboratory for a patient in-use, single actuation reproducibility study. The protocol detailing the experimental plan for this study is shown in Attachment 1. The purpose of this report is to summarize the results of this testing

II. Samples

All samples used the Bespak Valve #BK0080332, 0.05% PVP, and 10 % ethanol.

A1 – Inherent Water
A2 – 800 ppm Water
A3 – 1000 ppm Water
A4 – 1200 ppm Water
A5 – 1500 ppm Water
A6 – 2500 ppm Water

III. Test Procedures

TP- Water Content
TP- Dose Uniformity (US)
TP- Total Can Assay
Single Actuation Reproducibility – Experimental Procedure described in protocol
TP- , Valve Delivery Through Life – with modification described in protocol

Orientation	Canister Number	Beginning of Study (ppm)	End of Study (ppm)
Inverted	3	1388.0	1459.0
Inverted	4	1383.0	1612.0
Inverted	5	1375.0	1597.0
Upright	1	2724.0	1799.0
Upright	2	4774.0	1767.0
Upright	3	2347.0	1791.0
Upright	4	2318.0	1840.0
Upright	5	2277.0	1847.0
Inverted	1	2276.0	1877.0
Inverted	2	2365.0	2571.0
Inverted	3	2313.0	1781.0
Inverted	4	2333.0	2002.0
Inverted	5	2344.0	2572.0

B. Single Actuation Reproducibility after 6 Hour Delay

Ten canisters from each lot were tested for single actuation reproducibility following a 6 hour rest period after priming the canisters. Five canisters from each lot were stored upright and five canisters were stored inverted. The results for each lot are shown in Tables 2, 3, 4, 5, 6, and 7. The albuterol sulfate data from these tables was also compiled and is presented graphically in Figure 2.

For lots testing was discontinued after the first week. These lots exhibited the albuterol sulfate trend of being low for the first actuation 1 and high for the second actuation with a 6 hour rest after priming. The remaining lots do not exhibit this behavior and were tested through the life of the canister following the patient in use actuation protocol.

Table 2. Single Actuation Reproducibility for Lot
Upright and Inverted Samples, Inherent Water

	Albuterol Sulfate					
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	49.87	126.95	N/A	N/A	N/A	N/A
-Up-2	53.22	127.20	N/A	N/A	N/A	N/A
-Up-3	56.08	124.65	N/A	N/A	N/A	N/A
-Up-4	51.62	127.27	N/A	N/A	N/A	N/A
-Up-5	50.58	127.07	N/A	N/A	N/A	N/A
-Inv-1	78.10	151.04	N/A	N/A	N/A	N/A
-Inv-2	113.18	154.54	N/A	N/A	N/A	N/A
-Inv-3	88.07	174.11	N/A	N/A	N/A	N/A
-Inv-4	93.35	169.84	N/A	N/A	N/A	N/A
-Inv-5	70.53	161.62	N/A	N/A	N/A	N/A

	Ipratropium Bromide					
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	95.24	98.92	N/A	N/A	N/A	N/A
-Up-2	93.13	104.19	N/A	N/A	N/A	N/A
-Up-3	99.05	102.11	N/A	N/A	N/A	N/A
-Up-4	96.32	101.88	N/A	N/A	N/A	N/A
-Up-5	98.14	96.52	N/A	N/A	N/A	N/A
-Inv-1	92.54	95.59	N/A	N/A	N/A	N/A
-Inv-2	94.69	91.53	N/A	N/A	N/A	N/A
-Inv-3	89.15	100.92	N/A	N/A	N/A	N/A
-Inv-4	93.30	93.63	N/A	N/A	N/A	N/A
-Inv-5	96.02	101.16	N/A	N/A	N/A	N/A

Table 3. Single Actuation Reproducibility for Lot [redacted] Upright and Inverted Samples, 800 ppm Water

Albuterol Sulfate						
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
[redacted]-Up-1	48.60	137.69	N/A	N/A	N/A	N/A
[redacted]-Up-2	49.35	123.03	N/A	N/A	N/A	N/A
[redacted]-Up-3	59.65	123.56	N/A	N/A	N/A	N/A
[redacted]-Up-4	49.85	128.45	N/A	N/A	N/A	N/A
[redacted]-Up-5	45.63	128.28	N/A	N/A	N/A	N/A
[redacted]-Inv-1	89.50	137.83	N/A	N/A	N/A	N/A
[redacted]-Inv-2	63.97	145.05	N/A	N/A	N/A	N/A
[redacted]-Inv-3	71.63	122.67	N/A	N/A	N/A	N/A
[redacted]-Inv-4	75.94	126.01	N/A	N/A	N/A	N/A
[redacted]-Inv-5	65.85	137.82	N/A	N/A	N/A	N/A

Ipratropium Bromide						
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
[redacted]-Up-1	98.15	99.55	N/A	N/A	N/A	N/A
[redacted]-Up-2	97.86	96.72	N/A	N/A	N/A	N/A
[redacted]-Up-3	95.91	103.24	N/A	N/A	N/A	N/A
[redacted]-Up-4	98.77	97.53	N/A	N/A	N/A	N/A
[redacted]-Up-5	96.66	101.29	N/A	N/A	N/A	N/A
[redacted]-Inv-1	95.75	98.33	N/A	N/A	N/A	N/A
[redacted]-Inv-2	93.67	99.81	N/A	N/A	N/A	N/A
[redacted]-Inv-3	97.13	97.87	N/A	N/A	N/A	N/A
[redacted]-Inv-4	95.95	97.28	N/A	N/A	N/A	N/A
[redacted]-Inv-5	95.27	102.27	N/A	N/A	N/A	N/A

Table 4. Single Actuation Reproducibility for Lot ?
Upright and Inverted Samples, 1000 ppm Water

Albuterol Sulfate						
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	71.63	110.75	N/A	N/A	N/A	N/A
-Up-2	56.02	130.26	N/A	N/A	N/A	N/A
-Up-3	51.97	126.82	N/A	N/A	N/A	N/A
-Up-4	52.41	124.41	N/A	N/A	N/A	N/A
-Up-5	80.63	104.43	N/A	N/A	N/A	N/A
-Inv-1	63.38	128.71	N/A	N/A	N/A	N/A
-Inv-2	65.70	128.20	N/A	N/A	N/A	N/A
-Inv-3	73.37	118.64	N/A	N/A	N/A	N/A
-Inv-4	77.65	121.92	N/A	N/A	N/A	N/A
-Inv-5	66.54	126.07	N/A	N/A	N/A	N/A

Ipratropium Bromide						
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
)-Up-1	95.35	96.41	N/A	N/A	N/A	N/A
)-Up-2	96.43	99.95	N/A	N/A	N/A	N/A
-Up-3	97.69	97.97	N/A	N/A	N/A	N/A
-Up-4	93.75	99.16	N/A	N/A	N/A	N/A
-Up-5	95.13	96.11	N/A	N/A	N/A	N/A
-Inv-1	95.56	100.24	N/A	N/A	N/A	N/A
-Inv-2	96.95	100.28	N/A	N/A	N/A	N/A
-Inv-3	97.81	97.64	N/A	N/A	N/A	N/A
-Inv-4	97.71	98.70	N/A	N/A	N/A	N/A
-Inv-5	96.17	100.76	N/A	N/A	N/A	N/A

Table 5. Single Actuation Reproducibility for Lot Upright and Inverted Samples, 1200 ppm Water

Albuterol Sulfate						
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	86.90	101.85	73.64	121.92	77.48	117.68
-Up-2	83.30	109.16	102.60	112.36	74.93	129.79
-Up-3	81.19	103.54	85.34	109.31	42.86	138.37
-Up-4	82.84	105.98	84.58	113.64	52.09	136.79
-Up-5	56.30	122.20	59.94	137.12	54.41	135.15
-Inv-1	88.93	99.61	78.58	123.30	72.41	128.21
-Inv-2	72.10	119.88	82.73	120.10	80.84	117.92
-Inv-3	84.10	113.51	77.30	129.43	65.37	127.29
-Inv-4	84.54	106.97	90.35	113.30	69.43	120.71
-Inv-5	76.56	119.07	80.61	119.43	71.24	124.34

Ipratropium Bromide						
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	96.35	99.24	99.01	97.95	100.61	100.79
-Up-2	94.35	103.75	94.91	104.14	106.38	102.25
-Up-3	95.98	98.17	96.63	97.03	96.92	102.54
-Up-4	94.38	102.45	95.96	97.79	98.10	105.19
-Up-5	101.78	97.93	101.37	102.52	102.73	107.02
-Inv-1	96.39	90.19	98.51	100.59	101.58	108.76
-Inv-2	100.10	100.60	99.82	102.67	103.73	107.96
-Inv-3	97.16	100.60	97.18	104.34	100.07	108.32
-Inv-4	95.58	97.43	98.27	102.32	105.41	108.44
-Inv-5	99.50	100.52	101.33	101.25	103.10	106.07

Table 6. Single Actuation Reproducibility for Lot
Upright and Inverted Samples, 1500 ppm Water

Albuterol Sulfate						
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	94.62	99.02	102.73	110.10	101.00	108.91
-Up-2	92.30	101.31	100.62	105.94	91.17	112.39
-Up-3	94.41	101.03	99.17	116.08	101.08	107.24
-Up-4	95.39	99.19	95.33	105.99	92.86	109.29
-Up-5	98.04	100.37	95.85	110.52	89.44	110.49
-Inv-1	96.36	99.38	92.49	109.67	83.09	107.79
-Inv-2	94.78	105.63	93.82	116.65	85.19	117.40
-Inv-3	98.08	101.14	101.80	107.13	94.68	110.60
-Inv-4	94.92	101.36	94.04	108.36	88.57	108.73
-Inv-5	93.20	99.04	99.38	110.70	94.67	102.19

Ipratropium Bromide						
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	97.57	97.84	95.93	100.56	104.01	105.51
-Up-2	96.13	99.37	99.04	97.10	102.07	107.00
-Up-3	101.21	98.24	99.87	102.88	107.59	107.83
-Up-4	98.40	98.62	98.13	97.41	101.62	104.50
-Up-5	100.59	98.85	97.67	101.23	101.67	106.88
-Inv-1	97.29	98.37	94.27	102.27	91.78	105.21
-Inv-2	97.21	102.94	98.97	105.40	103.99	108.79
-Inv-3	100.14	100.35	97.97	101.26	102.20	107.54
-Inv-4	97.44	101.24	98.73	100.17	103.00	107.15
-Inv-5	95.39	97.97	95.20	101.44	99.90	106.96

Table 7. Single Actuation Reproducibility for Lot
Upright and Inverted Samples, 2500 ppm Water

Albuterol Sulfate						
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	95.51	96.18	93.06	106.82	89.02	98.71
-Up-2	91.40	98.26	97.25	100.72	91.40	96.23
-Up-3	97.37	98.65	99.53	96.12	90.59	103.09
-Up-4	95.08	95.98	91.04	103.12	79.05	103.87
-Up-5	95.89	100.90	104.42	95.22	92.35	100.06
-Inv-1	99.18	97.61	98.05	100.63	89.50	104.01
-Inv-2	98.00	99.87	103.83	105.87	87.10	97.13
-Inv-3	95.97	98.53	99.28	103.49	87.53	96.46
-Inv-4	97.42	97.94	95.65	102.85	88.18	97.42
-Inv-5	100.73	103.16	103.08	105.17	91.20	100.93

Ipratropium Bromide						
	Week 1		Week 2		Week 3	
Lot /Orientation/Can	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)	Actuation 1 (% of Theory)	Actuation 2 (% of Theory)
-Up-1	98.49	98.44	99.09	101.27	103.15	103.73
-Up-2	92.51	100.17	99.39	95.11	103.77	101.20
-Up-3	99.17	98.09	99.57	95.75	100.00	105.30
-Up-4	97.77	96.62	95.22	97.40	91.87	109.92
-Up-5	95.55	98.96	99.36	95.79	102.33	100.74
-Inv-1	98.09	99.33	97.88	100.19	102.34	110.94
-Inv-2	98.69	99.38	103.30	106.59	102.82	109.17
-Inv-3	94.24	101.02	96.22	103.06	100.14	108.23
-Inv-4	97.41	96.45	96.90	100.47	102.63	107.16
-Inv-5	96.72	102.32	102.22	105.63	104.23	110.85

C. Dose Uniformity after 6 Hour Delay

Ten canisters from each lot were tested for uniformity of dose (2 actuations) following a 6 hour rest period after priming the canisters. Five canisters from each lot were stored upright and five canisters were stored inverted. The results for each lot are shown in Tables 8, 9, 10, 11, 12, and 13. The albuterol sulfate data from these tables was also compiled and is presented graphically in Figures 3.

For lots testing was discontinued after the first week. These lots had exhibited poor single actuation reproducibility during the first week of testing. The remaining lots were tested through the life of the canister following the patient in use actuation protocol.

Table 8. Uniformity of Dose for Lot (Inherent Water), Upright and Inverted Samples

	Week 1		Week 2		Week 3	
Lot/Orientation/Can	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)
/Up/1	93.58	99.67	N/A	N/A	N/A	N/A
/Up/2	91.59	100.38	N/A	N/A	N/A	N/A
/Up/3	90.11	98.39	N/A	N/A	N/A	N/A
/Up/4	87.17	95.25	N/A	N/A	N/A	N/A
/Up/5	95.20	99.56	N/A	N/A	N/A	N/A
Inv/1	148.63	97.29	N/A	N/A	N/A	N/A
Inv/2	153.88	97.25	N/A	N/A	N/A	N/A
Inv/3	168.93	102.22	N/A	N/A	N/A	N/A
Inv/4	125.87	96.76	N/A	N/A	N/A	N/A
Inv/5	118.27	99.42	N/A	N/A	N/A	N/A

Table 9. Uniformity of Dose for Lot [redacted] (800 ppm Water), Upright and Inverted Samples

	Week 1		Week 2		Week 3	
Lot/Orientation/Can	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)
[redacted]/Up/1	100.61	98.52	N/A	N/A	N/A	N/A
/Up/2	88.43	98.38	N/A	N/A	N/A	N/A
/Up/3	95.12	98.97	N/A	N/A	N/A	N/A
/Up/4	89.92	96.90	N/A	N/A	N/A	N/A
/Up/5	88.60	97.17	N/A	N/A	N/A	N/A
/Inv/1	101.06	97.01	N/A	N/A	N/A	N/A
/Inv/2	102.17	97.76	N/A	N/A	N/A	N/A
/Inv/3	101.22	99.41	N/A	N/A	N/A	N/A
/Inv/4	105.29	97.20	N/A	N/A	N/A	N/A
/Inv/5	99.46	99.34	N/A	N/A	N/A	N/A

Table 10. Uniformity of Dose for Lot (1000 ppm Water), Upright and Inverted Samples

	Week 1		Week 2		Week 3	
Lot/Orientation/Can	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)
/Up/1	94.82	101.07	N/A	N/A	N/A	N/A
/Up/2	92.18	97.01	N/A	N/A	N/A	N/A
/Up/3	94.90	102.35	N/A	N/A	N/A	N/A
/Up/4	87.00	94.65	N/A	N/A	N/A	N/A
/Up/5	91.39	97.60	N/A	N/A	N/A	N/A
Inv/1	103.68	100.80	N/A	N/A	N/A	N/A
Inv/2	101.18	100.45	N/A	N/A	N/A	N/A
Inv/3	101.69	100.84	N/A	N/A	N/A	N/A
Inv/4	97.50	98.91	N/A	N/A	N/A	N/A
Inv/5	99.93	99.46	N/A	N/A	N/A	N/A

Table 11. Uniformity of Dose for Lot (1200 ppm Water), Upright and Inverted Samples

	Week 1		Week 2		Week 3	
Lot/Orientation/Can	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)
/Up/1	98.05	96.57	94.30	98.98	101.45	101.40
/Up/2	100.06	98.15	100.77	99.43	103.26	99.80
/Up/3	94.51	97.32	83.48	99.77	103.59	101.52
/Up/4	97.56	97.49	96.82	99.70	100.46	100.63
/Up/5	89.82	99.02	93.53	104.60	108.98	106.29
Inv/1	99.90	100.52	97.95	101.21	103.23	104.73
Inv/2	103.60	102.42	102.00	104.31	100.12	101.44
Inv/3	94.77	92.73	97.57	100.38	97.78	102.36
Inv/4	99.66	98.75	96.92	102.10	99.31	103.07
Inv/5	102.07	99.49	95.21	100.01	96.91	104.22

Table 12. Uniformity of Dose for Lot (1500 ppm Water), Upright and Inverted Samples

	Week 1		Week 2		Week 3	
Lot/Orientation/Can	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)
/Up/1	101.37	100.07	101.25	100.79	103.62	102.01
/Up/2	99.40	97.58	102.79	100.28	99.08	101.35
/Up/3	102.85	100.26	103.15	101.15	99.52	101.78
/Up/4	102.06	99.23	102.39	101.28	98.10	97.21
/Up/5	102.73	100.78	102.55	100.73	104.53	102.70
/Inv/1	99.48	99.40	98.77	100.67	100.56	101.62
/Inv/2	101.03	101.57	100.07	102.87	98.95	103.23
/Inv/3	103.35	101.23	100.68	101.15	102.45	101.75
/Inv/4	100.28	101.19	101.73	102.49	99.89	103.29
/Inv/5	99.35	99.52	100.22	101.33	99.13	102.28

Table 13. Uniformity of Dose for Lot (2500 ppm Water), Upright and Inverted Samples

	Week 1		Week 2		Week 3	
Lot/Orientation/Can	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)	Albuterol Sulfate (% of Theory)	Ipratropium Bromide (% of Theory)
Up/1	96.86	97.73	97.96	100.81	94.23	97.83
Up/2	102.17	98.49	95.56	98.81	91.56	91.38
Up/3	100.03	98.82	97.63	97.85	107.24	104.78
Up/4	100.72	102.19	97.81	100.22	89.04	92.07
Up/5	100.05	98.69	100.00	99.72	97.59	93.49
Inv/1	99.99	99.29	96.75	101.20	92.36	99.61
Inv/2	100.29	99.93	95.69	101.00	91.93	101.48
Inv/3	100.94	99.01	97.78	100.57	92.58	100.08
Inv/4	100.45	98.31	97.59	100.65	94.01	101.29
Inv/5	104.03	101.43	101.26	103.90	96.34	103.60

V. Conclusions

Water contents for all samples were in the expected ranges, although the measured results tended to be 100 – 150 ppm below target.

Single actuation results for lots with approximately 300 to 1000 ppm exhibited poor reproducibility between actuations at the beginning of the study. Testing on these canisters was discontinued after the first week of the study. Samples with 1200 ppm of water had only one can at the beginning of the study with poor reproducibility. Additional canisters from this lot started to exhibit poor reproducibility during the third week of the study. Samples with 1500 ppm water and 2500 ppm water exhibited good reproducibility between actuations throughout the study.

Dose uniformity results for all samples were within the expected ranges, with the exception of the inherent water inverted samples. These samples had 4 canisters out of 5 in excess of 125% of theory for drug delivery through the valve after a 6 hour pause. This trend was also observed for these canisters during single actuation reproducibility testing as well.

Total can assay results for the lots tested were within the expected range, with the exception of one inherent water inverted sample, which sprayed during sample preparation, resulting in low results for both albuterol sulfate and ipratropium bromide. This testing was added after the protocol was executed to confirm the analyte concentrations of the bulk solution in the canisters and that there were no losses in the metering chamber during actuation. There is good agreement of these results with the measured dose delivered through the valve, confirming that there is no loss occurring in the metering chamber during actuation.

The valve delivery results for all canisters tested were within expected ranges, with one exception for a canister near the end of the study, which was high and could not be explained. Since the value was high, it could not have been the result of a sticking valve, which produces low valve deliveries.

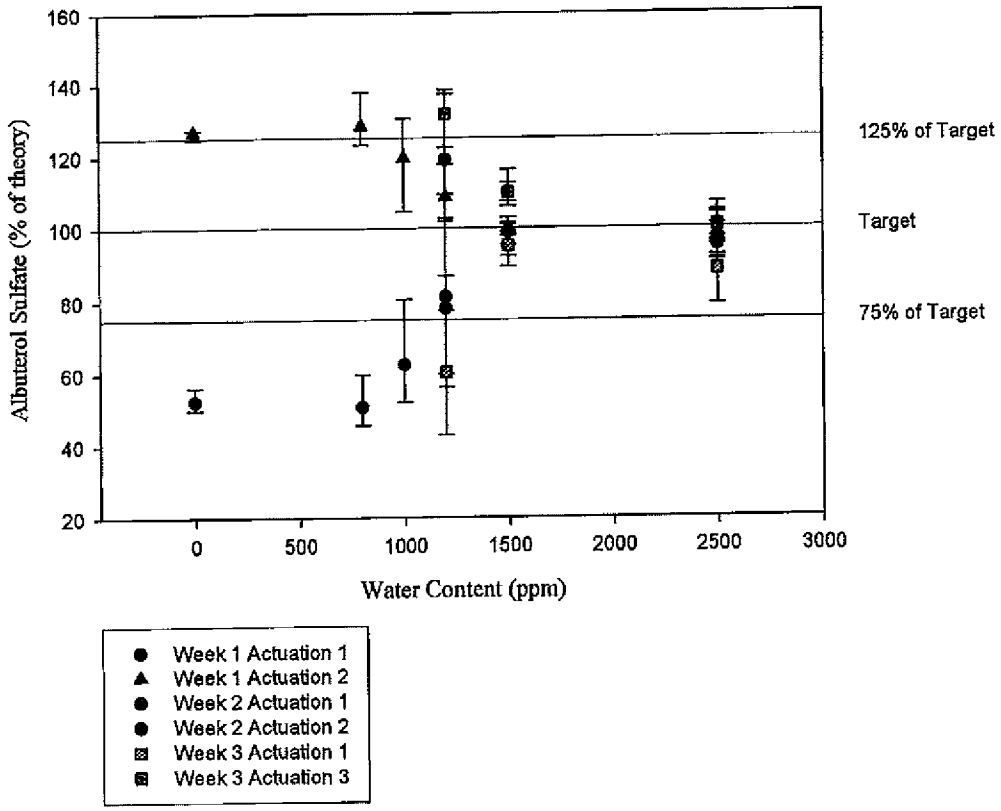

Figure 2: Single Actuation Reproducibility with 6 Hour Delay In Use – Albuterol Sulfate Results

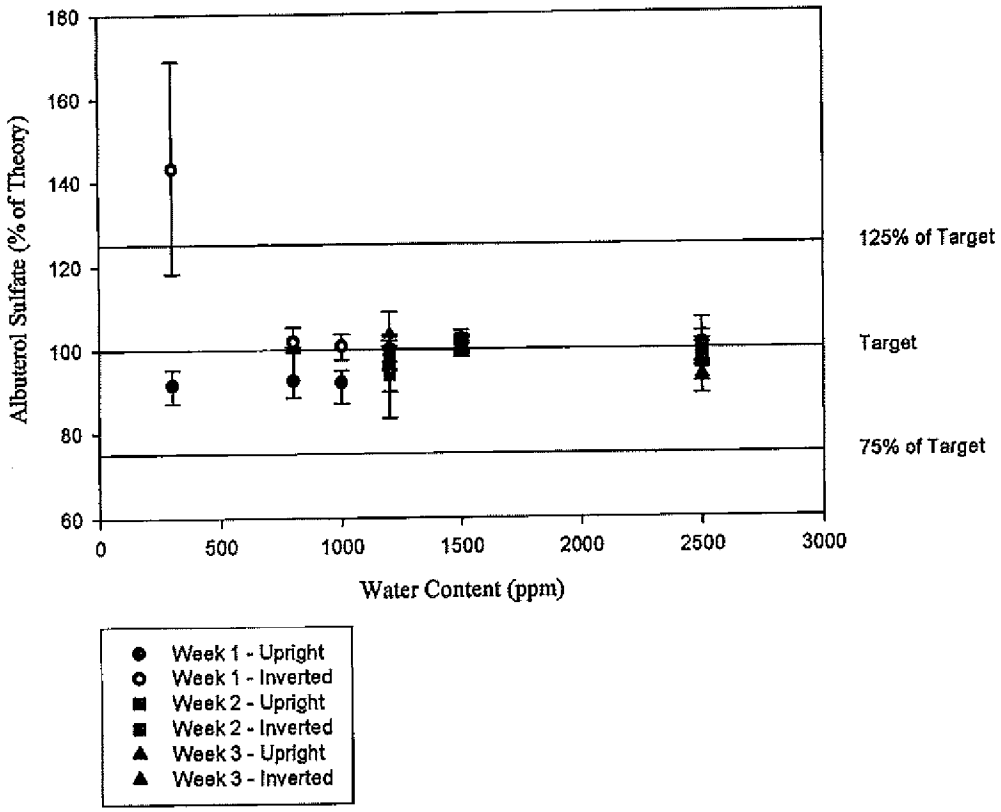

Figure 3: Uniformity of Dose with 6 Hour Delay In Use Study – Albuterol Sulfate Results

Attachment 1

Bespak 6 Hour Single Actuation and Dose through Life

Purpose:

The purpose of this protocol is to study the effect of water on single actuation reproducibility (SAR) and Dose through life (ca. 200 actuations). Samples were specially made to use the same concentrate, but have different water contents.

Samples:

AS Testing Number	Lot Number	Target ppm Water
AS 02-10-7515		Inherent
AS 02-10-7516		800
AS 02-10-7517		1000
AS 02-10-7518		1200
AS 02-10-7519		1500
AS 02-10-7520		2500

Five samples in each orientation (upright & Inverted) will be tested. This will result in a total of 60 canisters to be tested. Each canister will be tested according to the sampling protocol provided.

For all methods, calculate sample weights as follows: **W2-W1= Sample Weight**

W2 is the canister weight recorded immediately following each test point

W1 is the canister weight prior to testing (previous time point's W2.)

Wasting actuations will be performed using the alternate mouthpiece design. A delay of no less than 2 hours must occur between completion of previous wasting time point and

initiation of next wasting time point when multiple wasting sessions are required on the same day. Firing and shaking to be performed as outlined in the Uniformity of Dose procedure for wasting canisters. Do not clean the interior of the valve stem following wasting. Wasting will be performed per the provided sampling protocol.

Samples must equilibrate for 6 hours before any Uniformity of Dose sampling can be performed. The single actuation reproducibility protocol (SAR) requires that two single actuations be collected in separate containers where indicated. Do not shake canisters between the individual actuations for the SAR protocol. Uniformity of Dose samples will be collected per the provided sampling protocol.

If canisters containing lower levels of water (<1100 ppm) fail SAR during the first week of testing, then they will not be tested for the remainder of the study. Zero hour testing may be used to ensure that SAR failures are truly performance related.

Test Methods:

(Water) As per the sampling protocol below.

(Valve Delivery) With the exception that multiple actuations will be used for the determinations and multiple samples will be collected for each canister according to the sampling plan below. Weights will be recorded at the beginning of the study and after each actuation sequence

(Dose Uniformity) With the exception that samples will be collected after allowing the canisters to sit for 6 hours. Also samples will be collected using a single actuation reproducibility (SAR) protocol, which calls for allowing the sample to sit for 6 hours them collecting two single actuations in separate containers. Samples will be taken per the protocol below.

Start		
Day	**Actuation Number**	Action
Friday	1-5	Priming
	6-15	Clearing the Inlet tube
	16-20	Water Sample
Monday	21-24	Actuate to Waste Beg Day
	25&26	6 hr SAR *
	27-32	Actuate to Waste after SAR
Tuesday	33-36	Actuate to Waste Beg Day
	37-40	Actuate to Waste Mid Day
	41-44	Actuate to Waste End Day
Wednesday	45-48	Actuate to Waste Beg Day
	49&50	6 hr Dose *
	51-56	Actuate to Waste after Dose
Thursday	57-60	Actuate to Waste Beg Day
	61-64	Actuate to Waste Mid Day
	65-68	Actuate to Waste End Day
Friday	69-72	Actuate to Waste Beg Day
	73-76	Actuate to Waste Mid Day
	77-80	Actuate to Waste End Day

* 6 hrs after actuating to waste

Middle		
Day	**Actuation Number**	Action
Monday	81-84	Actuate to Waste Beg Day
	85-88	Actuate to Waste Mid Day
	89-92	Actuate to Waste End Day
Tuesday	93-96	Actuate to Waste Beg Day
	97&98	6 hr SAR *
	99-104	Actuate to Waste after SAR
Wednesday	105-108	Actuate to Waste Beg Day
	109&112	Actuate to Waste Mid Day
	113-116	Actuate to Waste End Day
Thursday	117-120	Actuate to Waste Beg Day
	121&122	6 hr Dose *
	123-128	Actuate to Waste after Dose
Friday	129-132	Actuate to Waste Beg Day
	133-136	Actuate to Waste Mid Day
	137-140	Actuate to Waste after SAR

* 6 hrs after actuating to waste

End		
Day	**Actuation Number**	Action
Monday	141-144	Actuate to Waste Beg Day
	145-148	Actuate to Waste Mid Day
	149-152	Actuate to Waste End Day
Tuesday	153-156	Actuate to Waste Beg Day
	157-160	Actuate to Waste Mid Day
	161-164	Actuate to Waste End Day
Wednesday	165-168	Actuate to Waste Beg Day
	169&170	6 hr Dose *
	171-174	Actuate to Waste after Dose
Thursday	175-178	Actuate to Waste Beg Day
	179-182	Actuate to Waste Mid Day
	183-186	Actuate to Waste End Day
Friday	187-190	Actuate to Waste Beg Day
	191&192	6 hr SAR *
Monday	193-202	Clear sample inlet tube
	203-207	Water – TP-00479

* 6 hrs after actuating to waste

Data Reporting:

Report the data using the Access Database provided.